

TRIPHASIL-21 - levonorgestrel and ethinyl estradiol

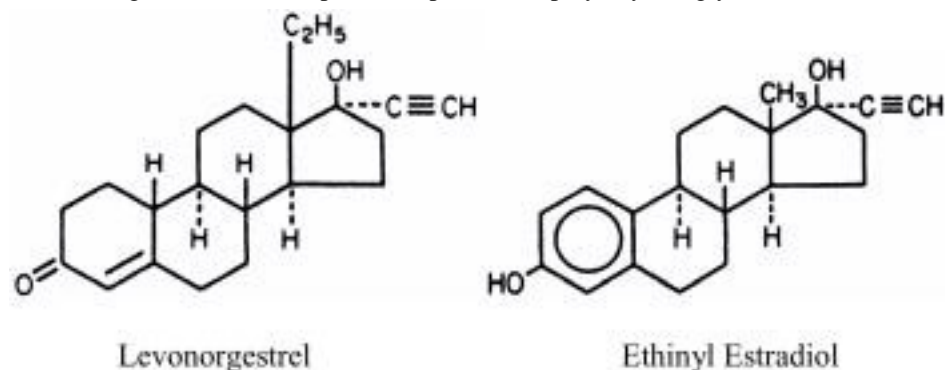
Wyeth-Ayest Company

Rx only

Patients should be counseled that this product does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

DESCRIPTION

Each Triphasil cycle of 21 tablets consists of three different drug phases as follows: Phase 1 comprised of 6 brown tablets, each containing 0.050 mg of levonorgestrel (d(-)-13 beta-ethyl-17-alpha-ethinyl-17-beta-hydroxygon-4-en-3-one), a totally synthetic progestogen, and 0.030 mg of ethinyl estradiol (19-nor-17 α -pregna-1,3,5(10)-trien-20-yne-3, 17-diol); phase 2 comprised of 5 white tablets, each containing 0.075 mg levonorgestrel and 0.040 mg ethinyl estradiol; and phase 3 comprised of 10 light-yellow tablets, each containing 0.125 mg levonorgestrel and 0.030 mg ethinyl estradiol. The inactive ingredients present are cellulose, iron oxides, lactose, magnesium stearate, polacrillin potassium, polyethylene glycol, titanium dioxide, and hydroxypropyl methylcellulose.



CLINICAL PHARMACOLOGY

Combination oral contraceptives primarily act by suppression of gonadotropins. Although the primary mechanism of this action is inhibition of ovulation, other alterations include changes in the cervical mucus (which increase the difficulty of sperm entry into the uterus) and the endometrium (which reduce the likelihood of implantation).

PHARMACOKINETICS

Absorption

Levonorgestrel is rapidly and completely absorbed after oral administration (bioavailability about 100%). Levonorgestrel is not subject to first-pass metabolism or enterohepatic circulation and therefore does not undergo variations in absorption after oral administration. Ethinyl estradiol is rapidly and almost completely absorbed from the gastrointestinal tract but, due to first-pass metabolism in gut mucosa and liver, the bioavailability of ethinyl estradiol is between 38% and 48%.

There have been no formal multiple-dose studies conducted using Triphasil. However, a multiple-dose study was done in 22 women using a monophasic, low dose combination of 0.10 mg levonorgestrel and 0.02 mg ethinyl estradiol. Maximum serum concentrations of levonorgestrel were found to be 2.8 ± 0.9 ng/mL (mean \pm SD) at 1.6 ± 0.9 hours after a single dose, reaching a steady state at day 19. Observed levonorgestrel concentrations increased from day 1 to days 6 and 21 by 34% and 96%, respectively. Unbound levonorgestrel concentrations subsequently increased from day 1 to days 6 and 21 by 25% and 83%, respectively, however, the accumulation of unbound levonorgestrel was approximately 14% less than total levonorgestrel accumulation. The kinetics of total levonorgestrel were non-linear due to an increase in binding of levonorgestrel to SHBG, which is attributed to increased SHBG levels that are induced by the daily administration of ethinyl estradiol. Ethinyl estradiol reached maximum serum concentrations of 62 ± 21 pg/mL at 1.5 ± 0.5 hours after a single dose, reaching steady state at day 6. Ethinyl estradiol concentrations increased by 19% from days 1 to 21 consistent with an elimination half-life of 18 hours.

Single-dose studies with Triphasil have been conducted with the following data reported below in Table I. Plasma concentrations have been corrected below to reflect single tablet dosing/day.

TABLE I: MEAN (SE) PHARMACOKINETIC PARAMETERS OF TRIPHASIL IN SINGLE-DOSE STUDIES

Levonorgestrel (LNG)				
Dose LNG/EE	C _{max}	t _{max}	t _{1/2}	AUC
μ g	ng/mL	h	h	ng•h/mL
50/30	1.7 (0.1)	1.3 (0.1)	23 (2.2)	17 (1.5)

75/40	2.1 (0.2)	1.5 (0.2)	15 (1.2)	21 (2.0)
125/30	2.5 (0.2)	1.6 (0.1)	23 (1.4)	34 (3.0)
Ethinyl Estradiol (EE)				
Dose LNG/EE	C _{max}	t _{max}	t _{1/2}	AUC
μg	pg/mL	h	h	pg•h/mL
50/30	141 (9)	1.4 (0.1)	8.1 (1.0)	1126 (113)
75/40	179 (13)	1.6 (0.2)	14 (1.7)	2177 (244)
125/30	115 (10)	1.5 (0.1)	8.8 (1.6)	1072 (170)

Distribution

Levonorgestrel is bound to SHBG and albumin. Levonorgestrel has high binding affinity for SHBG that is 60% of that of testosterone. Ethinyl estradiol is about 97% bound to plasma albumin. Ethinyl estradiol does not bind to SHBG, but will induce SHBG synthesis.

Metabolism

Levonorgestrel: The most important metabolic pathway occurs in the reduction of the $\Delta 4$ -3-oxo group and hydroxylation at positions 2 α , 1 β , and 16 β , followed by conjugation. Most of the metabolites that circulate in the blood are sulfates of 3 α ,5 β -tetrahydro-levonorgestrel, while excretion occurs predominately in the form of glucuronides. Some of the parent levonorgestrel also circulates as 17 β -sulfate. Metabolic clearance rates may differ among individuals by several-fold, and this may account in part for the wide variation observed in levonorgestrel concentrations among users.

Ethinyl estradiol: Cytochrome P450 enzymes (CYP3A4) in the liver are responsible for the 2-hydroxylation that is the major oxidative reaction. The 2-hydroxy metabolite is further transformed by methylation and glucuronidation prior to urinary and fecal excretion. Levels of Cytochrome P450 (CYP3A) vary widely among individuals and can explain the variation in rates of ethinyl estradiol 2-hydroxylation. Ethinyl estradiol is excreted in the urine and feces as glucuronide and sulfate conjugates, and undergoes enterohepatic circulation.

Excretion

The elimination half-life for levonorgestrel is approximately 36 ± 13 hours at steady state. Levonorgestrel and its metabolites are primarily excreted in the urine (40% to 68%) and about 16% to 48% are excreted in the feces. The elimination half-life of ethinyl estradiol is 18 ± 4.7 hours at steady state.

SPECIAL POPULATIONS

Hepatic Insufficiency

No formal studies have evaluated the effect of hepatic disease on the disposition of Triphasil. However, steroid hormones may be poorly metabolized in patients with impaired liver function.

Renal Insufficiency

No formal studies have evaluated the effect of renal disease on the disposition of Triphasil.

Drug-Drug Interactions

See “**Precautions**” section —**DRUG INTERACTIONS**.

INDICATIONS AND USAGE

Oral contraceptives are indicated for the prevention of pregnancy in women who elect to use this product as a method of contraception.

Oral contraceptives are highly effective. Table II lists the typical accidental pregnancy rates for users of combination oral contraceptives and other methods of contraception. The efficacy of these contraceptive methods, except sterilization and the IUD, depends upon the reliability with which they are used. Correct and consistent use of methods can result in lower failure rates.

TABLE II: PERCENTAGE OF WOMEN EXPERIENCING AN UNINTENDED PREGNANCY DURING THE FIRST YEAR OF USE OF A CONTRACEPTIVE METHOD

Method	Perfect Use	Typical Use
Levonorgestrel implants	0.05	0.05
Male sterilization	0.1	0.15
Female sterilization	0.5	0.5
Depo-Provera [®] (injectable progestogen)	0.3	0.3
Oral contraceptives		5

Combined	0.1	NA
Progestin only	0.5	NA
IUD		
Progesterone	1.5	2.0
Copper T 380A	0.6	0.8
Condom (male) without spermicide	3	14
(Female) without spermicide	5	21
Cervical cap		
Nulliparous women	9	20
Parous women	26	40
Vaginal sponge		
Nulliparous women	9	20
Parous women	20	40
Diaphragm with spermicidal cream or jelly	6	20
Spermicides alone (foam, creams, jellies, and vaginal suppositories)	6	26
Periodic abstinence (all methods)	1-9*	25
Withdrawal	4	19
No contraception (planned pregnancy)	85	85
NA - not available		
*Depending on method (calendar, ovulation, symptothermal, post-ovulation)		
Adapted from Hatcher RA et al, <i>Contraceptive Technology: 17th Revised Edition</i> . NY, NY: Ardent Media, Inc., 1998.		

Contraindications

Combination oral contraceptives should not be used in women with any of the following conditions:

Thrombophlebitis or thromboembolic disorders.

A past history of deep-vein thrombophlebitis or thromboembolic disorders.

Cerebral-vascular or coronary-artery disease.

Thrombogenic valvulopathies.

Thrombogenic rhythm disorders.

Diabetes with vascular involvement.

Uncontrolled hypertension.

Known or suspected carcinoma of the breast.

Carcinoma of the endometrium or other known or suspected estrogen-dependent neoplasia.

Undiagnosed abnormal genital bleeding.

Cholestatic jaundice of pregnancy or jaundice with prior pill use.

Hepatic adenomas or carcinomas, or active liver disease, as long as liver function has not returned to normal.

Known or suspected pregnancy.

Hypersensitivity to any of the components of Triphasil (levonorgestrel and ethinyl estradiol tablets—triphasic regimen).

WARNINGS

Cigarette smoking increases the risk of serious cardiovascular side effects from oral-contraceptive use. This risk increases with age and with the extent of smoking (in epidemiologic studies, 15 or more cigarettes per day was associated with a significantly increased risk) and is quite marked in women over 35 years of age. Women who use oral contraceptives should be strongly advised not to smoke.

The use of oral contraceptives is associated with increased risks of several serious conditions including venous and arterial thrombotic and thromboembolic events (such as myocardial infarction, thromboembolism, and stroke), hepatic neoplasia, gallbladder disease, and hypertension, although the risk of serious morbidity or mortality is very small in healthy women without underlying risk factors. The risk of morbidity and mortality increases significantly in the presence of other underlying risk factors such as certain inherited or acquired thrombophilias, hypertension, hyperlipidemias, obesity, and diabetes.

Practitioners prescribing oral contraceptives should be familiar with the following information relating to these risks.

The information contained in this package insert is based principally on studies carried out in patients who used oral contraceptives with higher formulations of estrogens and progestogens than those in common use today. The effect of long-term use of the oral contraceptives with lower formulations of both estrogens and progestogens remains to be determined.

Throughout this labeling, epidemiological studies reported are of two types: retrospective or case control studies and prospective or cohort studies. Case control studies provide a measure of the relative risk of disease, namely, a ratio of the incidence of a disease among oral-contraceptive users to that among nonusers. The relative risk does not provide information on the actual clinical occurrence of a disease. Cohort studies provide a measure of attributable risk, which is the difference in the incidence of disease between oral-contraceptive users and nonusers. The attributable risk does provide information about the actual occurrence of a disease in the population. For further information, the reader is referred to a text on epidemiological methods.

1. THROMBOEMBOLIC DISORDERS AND OTHER VASCULAR PROBLEMS

a. Myocardial infarction

An increased risk of myocardial infarction has been attributed to oral-contraceptive use. This risk is primarily in smokers or women with other underlying risk factors for coronary-artery disease such as hypertension, hypercholesterolemia, morbid obesity, and diabetes. The relative risk of heart attack for current oral-contraceptive users has been estimated to be two to six. The risk is very low under the age of 30.

Smoking in combination with oral-contraceptive use has been shown to contribute substantially to the incidence of myocardial infarctions in women in their mid-thirties or older with smoking accounting for the majority of excess cases. Mortality rates associated with circulatory disease have been shown to increase substantially in smokers over the age of 35 and nonsmokers over the age of 40 (Table III) among women who use oral contraceptives.

CIRCULATORY DISEASE MORTALITY RATES PER 100,000 WOMAN YEARS BY AGE, SMOKING STATUS AND ORAL-CONTRACEPTIVE USE

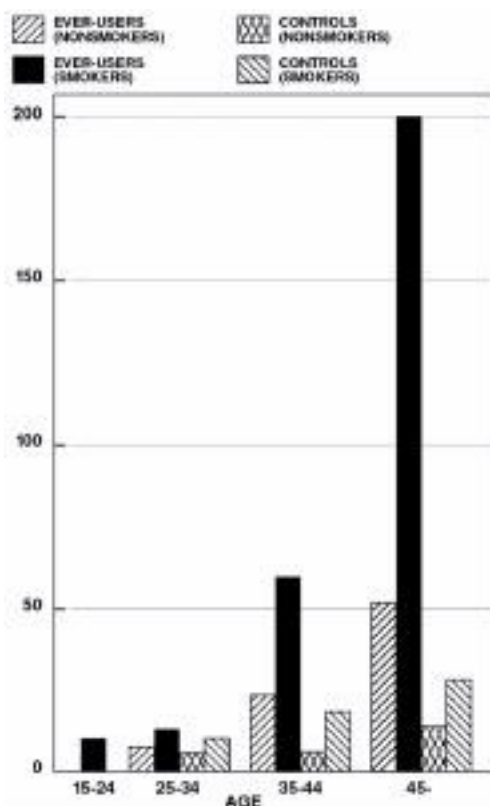


TABLE III. (Adapted from P.M. Layde and V. Beral, Lancet, 1:541-546, 1981.)

Oral contraceptives may compound the effects of well-known risk factors, such as hypertension, diabetes, hyperlipidemias, age, and obesity. In particular, some progestogens are known to decrease HDL cholesterol and cause glucose intolerance, while estrogens may create a state of hyperinsulinism. Oral contraceptives have been shown to increase blood pressure among users (see **section 9** in “Warnings”). Similar effects on risk factors have been associated with an increased risk of heart disease. Oral contraceptives must be used with caution in women with cardiovascular disease risk factors.

b. Thromboembolism

An increased risk of venous thromboembolic and thrombotic disease associated with the use of oral contraceptives is well established. Case control studies have found the relative risk of users compared to nonusers to be 3 for the first episode of superficial venous thrombosis, 4 to 11 for deep-vein thrombosis or pulmonary embolism, and 1.5 to 6 for women with predisposing conditions for venous thromboembolic disease. Cohort studies have shown the relative risk to be somewhat lower, about 3 for new cases and about 4.5 for new cases requiring hospitalization. The approximate incidence of deep-vein thrombosis and pulmonary embolism in users of low dose (<50 µg ethinyl estradiol) combination oral contraceptives is up to 4 per 10,000 woman-years compared to 0.5-3 per 10,000 woman-years for nonusers. However, the incidence is substantially less than that associated with pregnancy (6 per 10,000 woman-years). The risk of thromboembolic disease due to oral contraceptives is not related to length of use and disappears after pill use is stopped.

A two- to four-fold increase in relative risk of postoperative thromboembolic complications has been reported with the use of oral contraceptives. The relative risk of venous thrombosis in women who have predisposing conditions is twice that of women without such medical conditions. If feasible, oral contraceptives should be discontinued at least four weeks prior to and for two weeks after elective surgery of a type associated with an increase in risk of thromboembolism and during and following prolonged immobilization. Since the immediate postpartum period is also associated with an increased risk of thromboembolism, oral contraceptives should be started no earlier than four to six weeks after delivery in women who elect not to breast-feed, or a midtrimester pregnancy termination.

c. Cerebrovascular diseases

Oral contraceptives have been shown to increase both the relative and attributable risks of cerebrovascular events (thrombotic and hemorrhagic strokes), although, in general, the risk is greatest among older (>35 years), hypertensive women who also smoke. Hypertension was found to be a risk factor for both users and nonusers, for both types of strokes, while smoking interacted to increase the risk for hemorrhagic strokes.

In a large study, the relative risk of thrombotic strokes has been shown to range from 3 for normotensive users to 14 for users with severe hypertension. The relative risk of hemorrhagic stroke is reported to be 1.2 for nonsmokers who used oral contraceptives, 2.6 for smokers who did not use oral contraceptives, 7.6 for smokers who used oral contraceptives, 1.8 for normotensive users, and 25.7 for users with severe hypertension. The attributable risk is also greater in older women. Oral contraceptives also increase the risk for stroke in women with other underlying risk factors such as certain inherited or acquired thrombophilias, hyperlipidemias, and obesity.

Women with migraine (particularly migraine with aura) who take combination oral contraceptives may be at an increased risk of stroke.

d. Dose-related risk of vascular disease from oral contraceptives

A positive association has been observed between the amount of estrogen and progestogen in oral contraceptives and the risk of vascular disease. A decline in serum high-density lipoproteins (HDL) has been reported with many progestational agents. A decline in serum high-density lipoproteins has been associated with an increased incidence of ischemic heart disease. Because estrogens increase HDL cholesterol, the net effect of an oral contraceptive depends on a balance achieved between doses of estrogen and progestogen and the nature and absolute amount of progestogen used in the contraceptive. The amount of both hormones should be considered in the choice of an oral contraceptive.

Minimizing exposure to estrogen and progestogen is in keeping with good principles of therapeutics. For any particular estrogen/progestogen combination, the dosage regimen prescribed should be one which contains the least amount of estrogen and progestogen that is compatible with a low failure rate and the needs of the individual patient. New acceptors of oral-contraceptive agents should be started on preparations containing less than 50 mcg of estrogen.

e. Persistence of risk of vascular disease

There are two studies which have shown persistence of risk of vascular disease for ever-users of oral contraceptives. In a study in the United States, the risk of developing myocardial infarction after discontinuing oral contraceptives persists for at least 9 years for women 40 to 49 years who had used oral contraceptives for five or more years, but this increased risk was not demonstrated in other age groups. In another study in Great Britain, the risk of developing cerebrovascular disease persisted for at least 6 years after discontinuation of oral contraceptives, although excess risk was very small. However, both studies were performed with oral-contraceptive formulations containing 50 micrograms or higher of estrogens.

2. ESTIMATES OF MORTALITY FROM CONTRACEPTIVE USE

One study gathered data from a variety of sources which have estimated the mortality rate associated with different methods of contraception at different ages (Table IV). These estimates include the combined risk of death associated with contraceptive methods plus the risk attributable to pregnancy in the event of method failure. Each method of contraception has its specific benefits and risks. The study concluded that with the exception of oral-contraceptive users 35 and older who smoke and 40 and older who do not smoke, mortality associated with all methods of birth control is less than that associated with childbirth. The observation of a possible increase in risk of mortality with age for oral-contraceptive users is based on data gathered in the 1970's—but not reported until 1983. However, current clinical practice involves the use of lower estrogen dose formulations combined with careful restriction of oral-contraceptive use to women who do not have the various risk factors listed in this labeling.

Because of these changes in practice and, also, because of some limited new data which suggest that the risk of cardiovascular disease with the use of oral contraceptives may now be less than previously observed, the Fertility and Maternal Health Drugs Advisory Committee was asked to review the topic in 1989. The Committee concluded that although cardiovascular-disease risks may be increased with oral-contraceptive use after age 40 in healthy nonsmoking women (even with the newer low-dose formulations), there are greater potential health risks associated with pregnancy in older women and with the alternative surgical and medical procedures which may be necessary if such women do not have access to effective and acceptable means of contraception.

Therefore, the Committee recommended that the benefits of oral-contraceptive use by healthy nonsmoking women over 40 may outweigh the possible risks. Of course, older women, as all women who take oral contraceptives, should take the lowest possible dose formulation that is effective.

TABLE IV—ANNUAL NUMBER OF BIRTH-RELATED OR METHOD-RELATED DEATHS ASSOCIATED WITH CONTROL OF FERTILITY PER 100,000 NONSTERILE WOMEN, BY FERTILITY-CONTROL METHOD ACCORDING TO AGE

Method of control and outcome	15-19	20-24	25-29	30-34	35-39	40-44
No fertility-control methods*	7.0	7.4	9.1	14.8	25.7	28.2
Oral contraceptives nonsmoker**	0.3	0.5	0.9	1.9	13.8	31.6
Oral contraceptives smoker**	2.2	3.4	6.6	13.5	51.1	117.2
IUD**	0.8	0.8	1.0	1.0	1.4	1.4
Condom*	1.1	1.6	0.7	0.2	0.3	0.4

Diaphragm/ spermicide*	1.9	1.2	1.2	1.3	2.2	2.8
Periodic abstinence*	2.5	1.6	1.6	1.7	2.9	3.6
* Deaths are birth related						
** Deaths are method related						
Adapted from H.W. Ory, Family Planning Perspectives, 15:57-63, 1983.						

3. CARCINOMA OF THE REPRODUCTIVE ORGANS

A meta-analysis from 54 epidemiological studies reported that there is a slightly increased relative risk (RR=1.24) of having breast cancer diagnosed in women who are currently using combination oral contraceptives compared to never-users. The increased risk gradually disappears during the course of the 10 years after cessation of combination oral contraceptive use. These studies do not provide evidence for causation. The observed pattern of increased risk of breast cancer diagnosis may be due to earlier detection of breast cancer in combination oral contraceptive users, the biological effects of combination oral contraceptives, or a combination of both. Because breast cancer is rare in women under 40 years of age, the excess number of breast cancer diagnoses in current and recent combination oral contraceptive users is small in relation to the lifetime risk of breast cancer. Breast cancers diagnosed in ever-users tend to be less advanced clinically than the cancers diagnosed in never-users.

Some studies suggest that oral-contraceptive use has been associated with an increase in the risk of cervical intraepithelial neoplasia or invasive cervical cancer in some populations of women. However, there continues to be controversy about the extent to which such findings may be due to differences in sexual behavior and other factors.

In spite of many studies of the relationship between oral-contraceptive use and breast and cervical cancers, a cause-and-effect relationship has not been established.

4. HEPATIC NEOPLASIA

Benign hepatic adenomas are associated with oral-contraceptive use, although the incidence of benign tumors is rare in the United States. Indirect calculations have estimated the attributable risk to be in the range of 3.3 cases/100,000 for users, a risk that increases after four or more years of use. Rupture of rare, benign, hepatic adenomas may cause death through intra-abdominal hemorrhage. Studies from Britain have shown an increased risk of developing hepatocellular carcinoma in long-term (>8 years) oral-contraceptive users. However, these cancers are extremely rare in the U.S., and the attributable risk (the excess incidence) of liver cancers in oral-contraceptive users approaches less than one per million users.

5. OCULAR LESIONS

There have been clinical case reports of retinal thrombosis associated with the use of oral contraceptives that may lead to partial or complete loss of vision. Oral contraceptives should be discontinued if there is unexplained partial or complete loss of vision; onset of proptosis or diplopia; papilledema; or retinal vascular lesions. Appropriate diagnostic and therapeutic measures should be undertaken immediately.

6. ORAL-CONTRACEPTIVE USE BEFORE OR DURING EARLY PREGNANCY

Extensive epidemiological studies have revealed no increased risk of birth defects in women who have used oral contraceptives prior to pregnancy. Studies also do not suggest a teratogenic effect, particularly insofar as cardiac anomalies and limb-reduction defects are concerned, when taken inadvertently during early pregnancy (see “Contraindications” section).

The administration of oral contraceptives to induce withdrawal bleeding should not be used as a test for pregnancy. Oral contraceptives should not be used during pregnancy to treat threatened or habitual abortion.

It is recommended that for any patient who has missed two consecutive periods, pregnancy should be ruled out before continuing oral-contraceptive use. If the patient has not adhered to the prescribed schedule, the possibility of pregnancy should be considered at the time of the first missed period. Oral-contraceptive use should be discontinued if pregnancy is confirmed.

7. GALLBLADDER DISEASE

Earlier studies have reported an increased lifetime relative risk of gallbladder surgery in users of oral contraceptives and estrogens. More recent studies, however, have shown that the relative risk of developing gallbladder disease among oral-contraceptive users may be minimal. The recent findings of minimal risk may be related to the use of oral-contraceptive formulations containing lower hormonal doses of estrogens and progestogens.

8. CARBOHYDRATE AND LIPID METABOLIC EFFECTS

Oral contraceptives have been shown to cause glucose intolerance in a significant percentage of users. Oral contraceptives containing greater than 75 micrograms of estrogens cause hyperinsulinism, while lower doses of estrogen cause less glucose intolerance. Progestogens increase insulin secretion and create insulin resistance, this effect varying with different progestational agents. However, in the nondiabetic woman, oral contraceptives appear to have no effect on fasting blood glucose. Because of these demonstrated effects, prediabetic and diabetic women should be carefully observed while taking oral contraceptives.

A small proportion of women will have persistent hypertriglyceridemia while on the pill. As discussed earlier (see **“Warnings,” 1a. and 1d.**), changes in serum triglycerides and lipoprotein levels have been reported in oral-contraceptive users.

9. ELEVATED BLOOD PRESSURE

An increase in blood pressure has been reported in women taking oral contraceptives, and this increase is more likely in older oral-contraceptive users and with continued use. Data from the Royal College of General Practitioners and subsequent randomized trials have shown that the incidence of hypertension increases with increasing quantities of progestogens.

Women with a history of hypertension or hypertension-related diseases, or renal disease, should be encouraged to use another method of contraception. If women with hypertension elect to use oral contraceptives, they should be monitored closely, and if significant elevation of blood pressure occurs, oral contraceptives should be discontinued (see **“Contraindications”** section). For most women, elevated blood pressure will return to normal after stopping oral contraceptives, and there is no difference in the occurrence of hypertension among ever- and never-users.

10. HEADACHE

The onset or exacerbation of migraine or development of headache with a new pattern that is recurrent, persistent, or severe requires discontinuation of oral contraceptives and evaluation of the cause. (See **“Warnings,” 1c.**)

11. BLEEDING IRREGULARITIES

Breakthrough bleeding and spotting are sometimes encountered in patients on oral contraceptives, especially during the first three months of use. The type and dose of progestogen may be important. If bleeding persists or recurs, nonhormonal causes should be considered and adequate diagnostic measures taken to rule out malignancy or pregnancy in the event of breakthrough bleeding, as in the case of any abnormal vaginal bleeding. If pathology has been excluded, time or a change to another formulation may solve the problem. In the event of amenorrhea, pregnancy should be ruled out if the oral contraceptive has not been taken according to directions prior to the first missed withdrawal bleed or if two consecutive withdrawal bleeds have been missed.

Some women may encounter post-pill amenorrhea or oligomenorrhea (possibly with anovulation), especially when such a condition was preexistent.

PRECAUTIONS

1. GENERAL

Patients should be counseled that this product does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

2. PHYSICAL EXAMINATION AND FOLLOW-UP

A periodic personal and family medical history and complete physical examination are appropriate for all women, including women using oral contraceptives. The physical examination, however, may be deferred until after initiation of oral contraceptives if requested by the woman and judged appropriate by the clinician. The physical examination should include special reference to blood pressure, breasts, abdomen and pelvic organs, including cervical cytology, and relevant laboratory tests. In case of undiagnosed, persistent, or recurrent abnormal vaginal bleeding, appropriate measures should be conducted to rule out malignancy. Women with a strong family history of breast cancer or who have breast nodules should be monitored with particular care.

3. LIPID DISORDERS

Women who are being treated for hyperlipidemias should be followed closely if they elect to use oral contraceptives. Some progestogens may elevate LDL levels and may render the control of hyperlipidemias more difficult. (See **“Warnings,” 1d.**)

In patients with familial defects of lipoprotein metabolism receiving estrogen-containing preparations, there have been case reports of significant elevations of plasma triglycerides leading to pancreatitis.

4. LIVER FUNCTION

If jaundice develops in any woman receiving such drugs, the medication should be discontinued. Steroid hormones may be poorly metabolized in patients with impaired liver function.

5. FLUID RETENTION

Oral contraceptives may cause some degree of fluid retention. They should be prescribed with caution, and only with careful monitoring, in patients with conditions which might be aggravated by fluid retention.

6. EMOTIONAL DISORDERS

Patients becoming significantly depressed while taking oral contraceptives should stop the medication and use an alternate method of contraception in an attempt to determine whether the symptom is drug related.

Women with a history of depression should be carefully observed and the drug discontinued if depression recurs to a serious degree.

7. CONTACT LENSES

Contact-lens wearers who develop visual changes or changes in lens tolerance should be assessed by an ophthalmologist.

8. GASTROINTESTINAL MOTILITY

Diarrhea and/or vomiting may reduce hormone absorption.

9. DRUG INTERACTIONS

Interactions between ethinyl estradiol and other substances may lead to decreased or increased serum ethinyl estradiol concentrations. Decreased ethinyl estradiol plasma concentrations may cause an increased incidence of breakthrough bleeding and menstrual irregularities and may possibly reduce efficacy of the combination oral contraceptive. Reduced ethinyl estradiol concentrations have been associated with concomitant use of substances that induce hepatic microsomal enzymes, such as rifampin, rifabutin, barbiturates, phenylbutazone, phenytoin sodium, griseofulvin, topiramate, some protease inhibitors, modafinil, and possibly St. John's wort. Substances that may decrease plasma ethinyl estradiol concentrations by other mechanisms include any substance that reduces gut transit time and certain antibiotics (eg, ampicillin and other penicillins, tetracyclines) by a decrease of enterohepatic circulation of estrogens.

During concomitant use of ethinyl estradiol containing products and substances that may lead to decreased plasma steroid hormone concentrations, it is recommended that a nonhormonal back-up method of birth control be used in addition to the regular intake of Triphasil. If the use of a substance which leads to decreased ethinyl estradiol plasma concentrations is required for a prolonged period of time, combination oral contraceptives should not be considered the primary contraceptive.

After discontinuation of substances that may lead to decreased ethinyl estradiol plasma concentrations, use of a nonhormonal back-up method of birth control is recommended for 7 days. Longer use of a back-up method is advisable after discontinuation of substances that have led to induction of hepatic microsomal enzymes, resulting in decreased ethinyl estradiol concentrations. It may take several weeks until enzyme induction has completely subsided, depending on dosage, duration of use, and rate of elimination of the inducing substance.

Some substances may increase plasma ethinyl estradiol concentrations. These include:

- Competitive inhibitors for sulfation of ethinyl estradiol in the gastrointestinal wall, such as ascorbic acid (vitamin C) and acetaminophen.
- Substances that inhibit cytochrome P450 3A4 isoenzymes such as indinavir, fluconazole, and troleandomycin. Troleandomycin may increase the risk of intrahepatic cholestasis during coadministration with combination oral contraceptives.
- Atorvastatin (unknown mechanism).

Ethinyl estradiol may interfere with the mechanism of other drugs by inhibiting hepatic microsomal enzymes or by inducing hepatic drug conjugation, particularly glucuronidation. Accordingly, tissue concentrations may be either increased (eg, cyclosporine, theophylline, corticosteroids) or decreased.

The prescribing information of concomitant medications should be consulted to identify potential interactions.

10. INTERACTIONS WITH LABORATORY TESTS

Certain endocrine- and liver-function tests and blood components may be affected by oral contraceptives:

1. Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability.
2. Increased thyroid-binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T₄ by column or by radioimmunoassay. Free T₃ resin uptake is decreased, reflecting the elevated TBG; free T₄ concentration is unaltered.
3. Other binding proteins may be elevated in serum.
4. Sex-binding globulins are increased and result in elevated levels of total circulating sex steroids and corticoids; however, free or biologically active levels remain unchanged.
5. Triglycerides may be increased.
6. Glucose tolerance may be decreased.
7. Serum folate levels may be depressed by oral-contraceptive therapy. This may be of clinical significance if a woman becomes pregnant shortly after discontinuing oral contraceptives.

11. CARCINOGENESIS

See “Warnings” section.

12. PREGNANCY

Pregnancy Category X. See “**Contraindications**” and “**Warnings**” sections.

13. NURSING MOTHERS

Small amounts of oral-contraceptive steroids and/or metabolites have been identified in the milk of nursing mothers, and a few adverse effects on the child have been reported, including jaundice and breast enlargement. In addition, combination oral contraceptives given in the postpartum period may interfere with lactation by decreasing the quantity and quality of breast milk. If possible, the nursing mother should be advised not to use combination oral contraceptives but to use other forms of contraception until she has completely weaned her child.

14. PEDIATRIC USE

Safety and efficacy of Triphasil® (levonorgestrel and ethinyl estradiol tablets—triphasic regimen) have been established in women of reproductive age. Safety and efficacy are expected to be the same for postpubertal adolescents under the age of 16 and users 16 and older. Use of this product before menarche is not indicated.

INFORMATION FOR THE PATIENT

See Patient Labeling Printed Below.

ADVERSE REACTIONS

An increased risk of the following serious adverse reactions (see “**Warnings**” section for additional information) has been associated with the use of oral contraceptives:

Thromboembolic disorders and other vascular problems (including thrombophlebitis, arterial thromboembolism, pulmonary embolism, myocardial infarction, cerebral hemorrhage, cerebral thrombosis), carcinoma of the reproductive organs, hepatic neoplasia (including hepatic adenomas or benign liver tumors), ocular lesions (including retinal vascular thrombosis), gallbladder disease, carbohydrate and lipid effects, elevated blood pressure, and headache.

The following adverse reactions have been reported in patients receiving oral contraceptives and are believed to be drug related:

Nausea.

Vomiting.

Gastrointestinal symptoms (such as abdominal pain, cramps and bloating).

Breakthrough bleeding.

Spotting.

Change in menstrual flow.

Amenorrhea.

Temporary infertility after discontinuation of treatment.

Edema/fluid retention.

Melasma/chloasma which may persist.

Breast changes: tenderness, pain, enlargement, secretion.

Change in weight or appetite (increase or decrease).

Change in cervical erosion and secretion.

Diminution in lactation when given immediately postpartum.

Cholestatic jaundice.

Rash (allergic).

Mood changes, including depression.

Vaginitis, including candidiasis.

Change in corneal curvature (steepening).

Intolerance to contact lenses.

Mesenteric thrombosis.

Decrease in serum folate levels.

Exacerbation of systemic lupus erythematosus.

Exacerbation of porphyria.

Exacerbation of chorea.

Aggravation of varicose veins.

Anaphylactic/anaphylactoid reactions, including urticaria, angioedema, and severe reactions with respiratory and circulatory symptoms.

The following adverse reactions have been reported in users of oral contraceptives, and the association has been neither confirmed nor refuted:

Congenital anomalies.

Premenstrual syndrome.

Cataracts.

Optic neuritis, which may lead to partial or complete loss of vision.

Cystitis-like syndrome.

Nervousness.

Dizziness.

Hirsutism.

Loss of scalp hair.

Erythema multiforme.

Erythema nodosum.

Hemorrhagic eruption.

Impaired renal function.

Hemolytic uremic syndrome.

Budd-Chiari syndrome.

Acne.

Changes in libido.

Colitis.

Sickle-cell disease.

Cerebral-vascular disease with mitral valve prolapse.

Lupus-like syndromes.

Pancreatitis.

Dysmenorrhea.

OVERDOSAGE

Serious ill effects have not been reported following acute ingestion of large doses of oral contraceptives by young children. Overdosage may cause nausea, and withdrawal bleeding may occur in females.

NONCONTRACEPTIVE HEALTH BENEFITS

The following noncontraceptive health benefits related to the use of oral contraceptives are supported by epidemiological studies which largely utilized oral-contraceptive formulations containing doses exceeding 0.035 mg of ethinyl estradiol or 0.05 mg of mestranol.

Effects on menses:

Increased menstrual cycle regularity.

Decreased blood loss and decreased incidence of iron-deficiency anemia.

Decreased incidence of dysmenorrhea.

Effects related to inhibition of ovulation:

Decreased incidence of functional ovarian cysts.

Decreased incidence of ectopic pregnancies.

Effects from long-term use:

Decreased incidence of fibroadenomas and fibrocystic disease of the breast.

Decreased incidence of acute pelvic inflammatory disease.

Decreased incidence of endometrial cancer.

Decreased incidence of ovarian cancer.

DOSAGE AND ADMINISTRATION

To achieve maximum contraceptive effectiveness, Triphasil[®]-21 Tablets (levonorgestrel and ethinyl estradiol tablets—triphasic regimen) must be taken exactly as directed and at intervals not exceeding 24 hours.

Triphasil-21 Tablets are a three-phase preparation. The dosage of Triphasil-21 Tablets is one tablet daily for 21 consecutive days per menstrual cycle in the following order: 6 brown tablets (phase 1), followed by 5 white tablets (phase 2), and then followed by the last 10 light-yellow tablets (phase 3), according to the prescribed schedule. Tablets are then discontinued for 7 days (three weeks on, one week off). It is recommended that Triphasil-21 Tablets be taken at the same time each day, preferably after the evening meal or at bedtime. During the first cycle of medication, the patient should be instructed to take one Triphasil-21 Tablet daily in the order of 6 brown, 5 white and, finally, 10 light-yellow tablets, for twenty-one (21) consecutive days, beginning on day one (1) of her menstrual cycle. (The first day of menstruation is day one.) The tablets are then discontinued for one week (7 days). Withdrawal bleeding usually occurs within 3 days following discontinuation of Triphasil-21 Tablets and may not have finished before the next pack is started. (If Triphasil-21 Tablets are first taken later than the first day of the first menstrual cycle of medication or postpartum, contraceptive reliance should not be placed on Triphasil-21 Tablets until after the first 7 consecutive days of administration and a nonhormonal back-up method of birth control should be used during those 7 days. The possibility of ovulation and conception prior to initiation of medication should be considered.)

When switching from another oral contraceptive, Triphasil-21 Tablets should be started on the first day of bleeding following the last active tablet taken of the previous oral contraceptive. The patient may switch any day from a progestin-only pill and should begin Triphasil-21 the next day. If switching from an implant or injection, the patient should start Triphasil-21 on the day of implant removal or, if using an injection, the day the next injection would be due. In switching from a progestin-only pill, injection, or implant, the patient should be advised to use a nonhormonal back-up method of birth control for the first 7 days of tablet-taking.

The patient begins her next and all subsequent 21-day courses of Triphasil-21 Tablets on the same day of the week that she began her first course, following the same schedule: 21 days on — 7 days off. She begins taking her brown tablets on the 8th day after discontinuance, regardless of whether or not a menstrual period has occurred or is still in progress. Any time a subsequent cycle of Triphasil-21 Tablets is started later than the 8th day, the patient should be protected by another means of contraception until she has taken a tablet daily for seven consecutive days.

If spotting or breakthrough bleeding occurs, the patient is instructed to continue on the same regimen. This type of bleeding is usually transient and without significance; however, if the bleeding is persistent or prolonged, the patient is advised to consult her physician.

Although the occurrence of pregnancy is highly unlikely if Triphasil[®]-21 Tablets are taken according to directions, if withdrawal bleeding does not occur, the possibility of pregnancy must be considered. If the patient has not adhered to the prescribed schedule (missed one or more tablets or started taking them on a day later than she should have), the probability of pregnancy should be considered at the time of the first missed period and appropriate diagnostic measures taken before the medication is resumed. If the patient has adhered to the prescribed regimen and misses two consecutive periods, pregnancy should be ruled out before continuing the contraceptive regimen.

The risk of pregnancy increases with each tablet missed. For additional patient instructions regarding missed pills, see the “WHAT TO DO IF YOU MISS PILLS” section in the DETAILED PATIENT LABELING below. If breakthrough bleeding occurs following missed tablets, it will usually be transient and of no consequence.

Triphasil-21 may be initiated no earlier than day 28 postpartum in the non-lactating mother or after a second trimester abortion due to the increased risk for thromboembolism (see “**Contraindications**,” “**Warnings**,” and “**Precautions**” concerning thromboembolic disease). The patient should be advised to use a nonhormonal back-up method for the first 7 days of tablet-taking. However, if intercourse has already occurred, pregnancy should be excluded before the start of combined oral contraceptive use or the patient must wait for her first menstrual period. In the case of first-trimester abortion, if the patient starts Triphasil-21 immediately, additional contraceptive measures are not needed. It is to be noted that early resumption of ovulation may occur if Parlodel® (bromocriptine mesylate) has been used for the prevention of lactation.

HOW SUPPLIED

Triphasil®-21 Tablets (levonorgestrel and ethinyl estradiol tablets—triphasic regimen), NDC 0008-2535, are available in packages of 3 dial dispensers. Each cycle contains 21 round, coated tablets as follows:

NDC 0008-0641, six brown tablets marked “W” and “641”, each containing 0.050 mg levonorgestrel and 0.030 mg ethinyl estradiol; NDC 0008-0642, five white to off-white tablets marked “W” and “642”, each containing 0.075 mg levonorgestrel and 0.040 mg ethinyl estradiol; and

NDC 0008-0643, ten light-yellow tablets marked “W” and “643”, each containing 0.125 mg levonorgestrel and 0.030 mg ethinyl estradiol.

Store at controlled room temperature 20° to 25°C (68° to 77 °F).

References available upon request.

Brief Summary Patient Package Insert

This product (like all oral contraceptives) is intended to prevent pregnancy. It does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

Oral contraceptives, also known as “birth-control pills” or “the pill,” are taken to prevent pregnancy, and when taken correctly, have a failure rate of less than 1.0% per year when used without missing any pills. The average failure rate of large numbers of pill users is 5% per year when women who miss pills are included. For most women oral contraceptives are also free of serious or unpleasant side effects. However, forgetting to take pills considerably increases the chances of pregnancy.

For the majority of women, oral contraceptives can be taken safely. But there are some women who are at high risk of developing certain serious diseases that can be life-threatening or may cause temporary or permanent disability or death. The risks associated with taking oral contraceptives increase significantly if you:

- smoke.
- have high blood pressure, diabetes, high cholesterol, or a tendency to form blood clots, or are obese.
- have or have had clotting disorders, heart attack, stroke, angina pectoris, cancer of the breast or sex organs, jaundice, or malignant or benign liver tumors.

You should not take the pill if you suspect you are pregnant or have unexplained vaginal bleeding.

Cigarette smoking increases the risk of serious adverse effects on the heart and blood vessels from oral-contraceptive use. This risk increases with age and with the amount of smoking (15 or more cigarettes per day has been associated with a significantly increased risk) and is quite marked in women over 35 years of age. Women who use oral contraceptives should not smoke.

Most side effects of the pill are not serious. The most common such effects are nausea, vomiting, bleeding between menstrual periods, weight gain, breast tenderness, and difficulty wearing contact lenses. These side effects, especially nausea and vomiting, may subside within the first three months of use.

The serious side effects of the pill occur very infrequently, especially if you are in good health and do not smoke. However, you should know that the following medical conditions have been associated with or made worse by the pill:

1. Blood clots in the legs (thrombophlebitis), lungs (pulmonary embolism), stoppage or rupture of a blood vessel in the brain (stroke), blockage of blood vessels in the heart (heart attack and angina pectoris) or other organs of the body. As mentioned above, smoking increases the risk of heart attacks and strokes and subsequent serious medical consequences. Women with migraine also may be at increased risk of stroke.
2. Liver tumors, which may rupture and cause severe bleeding. A possible but not definite association has been found with the pill and liver cancer. However, liver cancers are extremely rare. The chance of developing liver cancer from using the pill is thus even rarer.
3. High blood pressure, although blood pressure usually returns to normal when the pill is stopped.

The symptoms associated with these serious side effects are discussed in the detailed leaflet given to you with your supply of pills. Notify your doctor or health-care provider if you notice any unusual physical disturbances while taking the pill. In addition, drugs

such as rifampin, as well as some anticonvulsants and some antibiotics, and possibly St. John's wort, may decrease oral-contraceptive effectiveness.

Breast cancer has been diagnosed slightly more often in women who use the pill than in women of the same age who do not use the pill. This very small increase in the number of breast cancer diagnoses gradually disappears during the 10 years after stopping use of the pill. It is not known whether the difference is caused by the pill. It may be that women taking the pill were examined more often, so that breast cancer was more likely to be detected.

Some studies have found an increase in the incidence of cancer or precancerous lesions of the cervix in women who use the pill. However, this finding may be related to factors other than the use of the pill.

Taking the pill provides some important noncontraceptive benefits. These include less painful menstruation, less menstrual blood loss and anemia, fewer pelvic infections, and fewer cancers of the ovary and the lining of the uterus.

Be sure to discuss any medical condition you may have with your health-care provider. Your health-care provider will take a medical and family history before prescribing oral contraceptives and will examine you. The physical examination may be delayed to another time if you request it and the health-care provider believes that it is appropriate to postpone it. You should be reexamined at least once a year while taking oral contraceptives. The detailed patient information leaflet gives you further information which you should read and discuss with your health-care provider.

This product (like all oral contraceptives) is intended to prevent pregnancy. It does not protect against transmission of HIV (AIDS) and other sexually transmitted diseases such as chlamydia, genital herpes, genital warts, gonorrhea, hepatitis B, and syphilis.

DETAILED PATIENT LABELING

This product (like all oral contraceptives) is intended to prevent pregnancy. It does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

INTRODUCTION

Any woman who considers using oral contraceptives (the birth-control pill or the pill) should understand the benefits and risks of using this form of birth control. This leaflet will give you much of the information you will need to make this decision and will also help you determine if you are at risk of developing any of the serious side effects of the pill. It will tell you how to use the pill properly so that it will be as effective as possible. However, this leaflet is not a replacement for a careful discussion between you and your health-care provider. You should discuss the information provided in this leaflet with him or her, both when you first start taking the pill and during your revisits. You should also follow your health-care provider's advice with regard to regular check-ups while you are on the pill.

EFFECTIVENESS OF ORAL CONTRACEPTIVES

Oral contraceptives or "birth-control pills" or "the pill" are used to prevent pregnancy and are more effective than other nonsurgical methods of birth control. When they are taken correctly, the chance of becoming pregnant is less than 1.0% when used perfectly, without missing any pills. Average failure rates are 5% per year. The chance of becoming pregnant increases with each missed pill during the menstrual cycle.

In comparison, average failure rates for other nonsurgical methods of birth control during the first year of use are as follows:

TABLE: PERCENTAGE OF WOMEN EXPERIENCING AN UNINTENDED PREGNANCY DURING THE FIRST YEAR OF USE OF A CONTRACEPTIVE METHOD

Method	Perfect Use	Average Use
Levonorgestrel implants	0.05	0.05
Male sterilization	0.1	0.15
Female sterilization	0.5	0.5
Depo-Provera [®] (injectable progestogen)	0.3	0.3
Oral contraceptives		5
Combined	0.1	NA
Progestin only	0.5	NA
IUD		
Progesterone	1.5	2.0
Copper T 380A	0.6	0.8
Condom (male) without spermicide	3	14
(female) without spermicide	5	21
Cervical cap		
Never given birth	9	20
Given birth	26	40
Vaginal sponge		
Never given birth	9	20

Given birth	20	40
Diaphragm with spermicidal cream or jelly	6	20
Spermicides alone (foam, creams, jellies, and vaginal suppositories)	6	26
Periodic abstinence (all methods)	1-9*	25
Withdrawal	4	19
No contraception (planned pregnancy)	85	85

NA - not available

*Depending on method (calendar, ovulation, symptothermal, post-ovulation)

Adapted from Hatcher RA et al, *Contraceptive Technology: 17th Revised Edition*. NY, NY: Ardent Media, Inc., 1998.

WHO SHOULD NOT TAKE ORAL CONTRACEPTIVES

Cigarette smoking increases the risk of serious adverse effects on the heart and blood vessels from oral-contraceptive use. This risk increases with age and with the amount of smoking (15 or more cigarettes per day has been associated with a significantly increased risk) and is quite marked in women over 35 years of age. Women who use oral contraceptives should not smoke.

Some women should not use the pill. For example, you should not take the pill if you are pregnant or think you may be pregnant. You should also not use the pill if you have had any of the following conditions:

- Heart attack or stroke
- Blood clots in the legs (thrombophlebitis), lungs (pulmonary embolism), or eyes.
- Blood clots in the deep veins of your legs.
- Known or suspected breast cancer or cancer of the lining of the uterus, cervix, or vagina or certain hormonally-sensitive cancers.
- Liver tumor (benign or cancerous).

Or, if you have any of the following:

- Chest pain (angina pectoris).
- Unexplained vaginal bleeding (until a diagnosis is reached by your doctor).
- Yellowing of the whites of the eyes or of the skin (jaundice) during pregnancy or during previous use of the pill.
- Known or suspected pregnancy.
- Heart valve or heart rhythm disorders that may be associated with formation of blood clots.
- Diabetes affecting your circulation.
- Uncontrolled high blood pressure.
- Active liver disease with abnormal liver function tests.
- Allergy or hypersensitivity to any of the components of Triphasil (levonorgestrel and ethinyl estradiol tablets—triphasic regimen).

Tell your health-care provider if you have ever had any of these conditions. Your health-care provider can recommend another method of birth control.

OTHER CONSIDERATIONS BEFORE TAKING ORAL CONTRACEPTIVES

Tell your health-care provider if you or any family member has ever had:

- Breast nodules, fibrocystic disease of the breast, an abnormal breast X-ray or mammogram.
- Diabetes.
- Elevated cholesterol or triglycerides.
- High blood pressure.
- A tendency to form blood clots.
- Migraine or other headaches or epilepsy.
- Mental depression.
- Gallbladder, heart, or kidney disease.
- History of scanty or irregular menstrual periods.

Women with any of these conditions should be checked often by their health-care provider if they choose to use oral contraceptives. Also, be sure to inform your doctor or health-care provider if you smoke or are on any medications.

RISKS OF TAKING ORAL CONTRACEPTIVES

1. Risk of developing blood clots

Blood clots and blockage of blood vessels are the most serious side effects of taking oral contraceptives and can be fatal. In particular, a clot in the legs can cause thrombophlebitis and a clot that travels to the lungs can cause a sudden blocking of the vessel carrying blood to the lungs. Rarely, clots occur in the blood vessels of the eye and may cause blindness, double vision, or impaired vision.

If you take oral contraceptives and need elective surgery, need to stay in bed for a prolonged illness, or have recently delivered a baby, you may be at risk of developing blood clots. You should consult your doctor about stopping oral contraceptives three to

four weeks before surgery and not taking oral contraceptives for two weeks after surgery or during bed rest. You should also not take oral contraceptives soon after delivery of a baby or a midtrimester pregnancy termination. It is advisable to wait for at least four weeks after delivery if you are not breast-feeding. If you are breast-feeding, you should wait until you have weaned your child before using the pill. (See also the section on breast-feeding in “General Precautions.”)

2. *Heart attacks and strokes*

Oral contraceptives may increase the tendency to develop strokes (stoppage or rupture of blood vessels in the brain) and angina pectoris and heart attacks (blockage of blood vessels in the heart). Any of these conditions can cause death or serious disability. Smoking greatly increases the possibility of suffering heart attacks and strokes. Furthermore, smoking and the use of oral contraceptives greatly increase the chances of developing and dying of heart disease.

Women with migraine (especially migraine with aura) who take oral contraceptives also may be at higher risk of stroke.

3. *Gallbladder disease*

Oral-contraceptive users probably have a greater risk than nonusers of having gallbladder disease, although this risk may be related to pills containing high doses of estrogens.

4. *Liver tumors*

In rare cases, oral contraceptives can cause benign but dangerous liver tumors. These benign liver tumors can rupture and cause fatal internal bleeding. In addition, a possible but not definite association has been found with the pill and liver cancers in two studies in which a few women who developed these very rare cancers were found to have used oral contraceptives for long periods. However, liver cancers are extremely rare. The chance of developing liver cancer from using the pill is thus even rarer.

5. *Cancer of the reproductive organs*

Breast cancer has been diagnosed slightly more often in women who use the pill than in women of the same age who do not use the pill. This very small increase in the number of breast cancer diagnoses gradually disappears during the 10 years after stopping use of the pill. It is not known whether the difference is caused by the pill. It may be that women taking the pill were examined more often, so that breast cancer was more likely to be detected.

Some studies have found an increase in the incidence of cancer or precancerous lesions of the cervix in women who use oral contraceptives. However, this finding may be related to factors other than the use of oral contraceptives.

6. *Lipid metabolism and inflammation of the pancreas*

In patients with inherited defects of lipid metabolism, there have been reports of significant elevations of plasma triglycerides during estrogen therapy. This has led to pancreatitis in some cases.

ESTIMATED RISK OF DEATH FROM A BIRTH-CONTROL METHOD OR PREGNANCY

All methods of birth control and pregnancy are associated with a risk of developing certain diseases which may lead to disability or death. An estimate of the number of deaths associated with different methods of birth control and pregnancy has been calculated and is shown in the following table.

ANNUAL NUMBER OF BIRTH-RELATED OR METHOD-RELATED DEATHS ASSOCIATED WITH CONTROL OF FERTILITY PER 100,000 NONSTERILE WOMEN, BY FERTILITY-CONTROL METHOD ACCORDING TO AGE

Method of control and outcome	15-19	20-24	25-29	30-34	35-39	40-44
No fertility control methods*	7.0	7.4	9.1	14.8	25.7	28.2
Oral contraceptives nonsmoker**	0.3	0.5	0.9	1.9	13.8	31.6
Oral contraceptives smoker**	2.2	3.4	6.6	13.5	51.1	117.2
IUD**	0.8	0.8	1.0	1.0	1.4	1.4
Condom*	1.1	1.6	0.7	0.2	0.3	0.4
Diaphragm/spermicide*	1.9	1.2	1.2	1.3	2.2	2.8
Periodic abstinence*	2.5	1.6	1.6	1.7	2.9	3.6

* Deaths are birth related

** Deaths are method related

In the above table, the risk of death from any birth-control method is less than the risk of childbirth, except for oral-contraceptive users over the age of 35 who smoke and pill users over the age of 40 even if they do not smoke. It can be seen in the table that for women

aged 15 to 39, the risk of death was highest with pregnancy (7 to 26 deaths per 100,000 women, depending on age). Among pill users who do not smoke, the risk of death was always lower than that associated with pregnancy for any age group, except for those women over the age of 40, when the risk increases to 32 deaths per 100,000 women, compared to 28 associated with pregnancy at that age. However, for pill users who smoke and are over the age of 35, the estimated number of deaths exceeds those for other methods of birth control. If a woman is over the age of 40 and smokes, her estimated risk of death is four times higher (117/100,000 women) than the estimated risk associated with pregnancy (28/100,000 women) in that age group.

The suggestion that women over 40 who don't smoke should not take oral contraceptives is based on information from older high-dose pills and on less-selective use of pills than is practiced today. An Advisory Committee of the FDA discussed this issue in 1989 and recommended that the benefits of oral-contraceptive use by healthy, nonsmoking women over 40 years of age may outweigh the possible risks. However, all women, especially older women, are cautioned to use the lowest-dose pill that is effective.

WARNING SIGNALS

If any of these adverse effects occur while you are taking oral contraceptives, call your doctor immediately:

- Sharp chest pain, coughing of blood, or sudden shortness of breath (indicating a possible clot in the lung).
- Pain in the calf (indicating a possible clot in the leg).
- Crushing chest pain or heaviness in the chest (indicating a possible heart attack).
- Sudden severe headache or vomiting, dizziness or fainting, disturbances of vision or speech, weakness, or numbness in an arm or leg (indicating a possible stroke).
- Sudden partial or complete loss of vision (indicating a possible clot in the eye).
- Breast lumps (indicating possible breast cancer or fibrocystic disease of the breast; ask your doctor or health-care provider to show you how to examine your breasts).
- Severe pain or tenderness in the stomach area (indicating a possibly ruptured liver tumor).
- Difficulty in sleeping, weakness, lack of energy, fatigue, or change in mood (possibly indicating severe depression).
- Jaundice or a yellowing of the skin or eyeballs, accompanied frequently by fever, fatigue, loss of appetite, dark-colored urine, or light-colored bowel movements (indicating possible liver problems).

SIDE EFFECTS OF ORAL CONTRACEPTIVES

1. *Vaginal bleeding*

Irregular vaginal bleeding or spotting may occur while you are taking the pills. Irregular bleeding may vary from slight staining between menstrual periods to breakthrough bleeding which is a flow much like a regular period. Irregular bleeding occurs most often during the first few months of oral-contraceptive use, but may also occur after you have been taking the pill for some time. Such bleeding may be temporary and usually does not indicate any serious problems. It is important to continue taking your pills on schedule. If the bleeding occurs in more than one cycle or lasts for more than a few days, talk to your doctor or health-care provider.

2. *Contact lenses*

If you wear contact lenses and notice a change in vision or an inability to wear your lenses, contact your doctor or health-care provider.

3. *Fluid retention*

Oral contraceptives may cause edema (fluid retention) with swelling of the fingers or ankles and may raise your blood pressure. If you experience fluid retention, contact your doctor or health-care provider.

4. *Melasma*

A spotty darkening of the skin is possible, particularly of the face.

5. *Other side effects*

Other side effects may include nausea, breast tenderness, change in appetite, headache, nervousness, depression, dizziness, loss of scalp hair, rash, vaginal infections, inflammation of the pancreas, and allergic reactions.

If any of these side effects bother you, call your doctor or health-care provider.

GENERAL PRECAUTIONS

1. *Missed periods and use of oral contraceptives before or during early pregnancy*

There may be times when you may not menstruate regularly after you have completed taking a cycle of pills. If you have taken your pills regularly and miss one menstrual period, continue taking your pills for the next cycle but be sure to inform your health-

care provider before doing so. If you have not taken the pills daily as instructed and missed a menstrual period, or if you missed two consecutive menstrual periods, you may be pregnant. Check with your health-care provider immediately to determine whether you are pregnant. Do not continue to take oral contraceptives until you are sure you are not pregnant, but continue to use another method of contraception.

There is no conclusive evidence that oral-contraceptive use is associated with an increase in birth defects when taken inadvertently during early pregnancy. Previously, a few studies had reported that oral contraceptives might be associated with birth defects, but these studies have not been confirmed. Nevertheless, oral contraceptives or any other drugs should not be used during pregnancy unless clearly necessary and prescribed by your doctor. You should check with your doctor about risks to your unborn child of any medication taken during pregnancy.

2. *While breast-feeding*

If you are breast-feeding, consult your doctor before starting oral contraceptives. Some of the drug will be passed on to the child in the milk. A few adverse effects on the child have been reported, including yellowing of the skin (jaundice) and breast enlargement. In addition, oral contraceptives may decrease the amount and quality of your milk. If possible, do not use oral contraceptives while breast-feeding. You should use another method of contraception since breast-feeding provides only partial protection from becoming pregnant, and this partial protection decreases significantly as you breast-feed for longer periods of time. You should consider starting oral contraceptives only after you have weaned your child completely.

3. *Laboratory tests*

If you are scheduled for any laboratory tests, tell your doctor you are taking birth-control pills. Certain blood tests may be affected by birth-control pills.

4. *Drug interactions*

Certain drugs may interact with birth-control pills to make them less effective in preventing pregnancy or cause an increase in breakthrough bleeding. Such drugs include rifampin, drugs used for epilepsy such as barbiturates (for example, phenobarbital) and phenytoin (Dilantin[®] is one brand of this drug) primidone (Mysoline[®]), topiramate (Topamax[®]), phenylbutazone (Butazolidin[®] is one brand) some drugs used for HIV such as ritonavir (Norvir[®]), modafinil (Provigil[®]), and possibly certain antibiotics (such as ampicillin and other penicillins, and tetracyclines) and St. John's wort. You may need to use an additional method of contraception during any cycle in which you take drugs that can make oral contraceptives less effective.

You may be at higher risk of a specific type of liver dysfunction if you take troleandomycin and oral contraceptives at the same time.

You should inform your health-care provider about all medicines you are taking, including nonprescription products.

5. *Sexually transmitted diseases*

This product (like all oral contraceptives) is intended to prevent pregnancy. It does not protect against transmission of HIV (AIDS) and other sexually transmitted diseases such as chlamydia, genital herpes, genital warts, gonorrhea, hepatitis B, and syphilis.

HOW TO TAKE THE PILL

IMPORTANT POINTS TO REMEMBER

BEFORE YOU START TAKING YOUR PILLS:

1. *BE SURE TO READ THESE DIRECTIONS:*

Before you start taking your pills.

Anytime you are not sure what to do.

2. *THE RIGHT WAY TO TAKE THE PILL IS TO TAKE ONE PILL EVERY DAY AT THE SAME TIME.*

If you miss pills you could get pregnant. This includes starting the pack late. The more pills you miss, the more likely you are to get pregnant.

3. *MANY WOMEN HAVE SPOTTING OR LIGHT BLEEDING, OR MAY FEEL SICK TO THEIR STOMACH DURING THE FIRST 1-3 PACKS OF PILLS.*

If you feel sick to your stomach, do not stop taking the pill. The problem will usually go away. If it doesn't go away, check with your doctor or clinic.

4. *MISSING PILLS CAN ALSO CAUSE SPOTTING OR LIGHT BLEEDING, even when you make up these missed pills.*

On the days you take 2 pills to make up for missed pills, you could also feel a little sick to your stomach.

5. *IF YOU HAVE VOMITING (within 3 to 4 hours after you take your pill), you should follow the instructions for **WHAT TO DO IF YOU MISS PILLS**. IF YOU HAVE DIARRHEA or IF YOU TAKE SOME MEDICINES, including some antibiotics, your pills may not work as well.*

Use a back-up method (such as condoms, spermicide, or sponge) until you check with your doctor or clinic.

6. *IF YOU HAVE TROUBLE REMEMBERING TO TAKE THE PILL*, talk to your doctor or clinic about how to make pill-taking easier or about using another method of birth control.
7. *IF YOU HAVE ANY QUESTIONS OR ARE UNSURE ABOUT THE INFORMATION IN THIS LEAFLET*, call your doctor or clinic.

BEFORE YOU START TAKING YOUR PILLS

1. **DECIDE WHAT TIME OF DAY YOU WANT TO TAKE YOUR PILL.**

It is important to take it at about the same time every day.

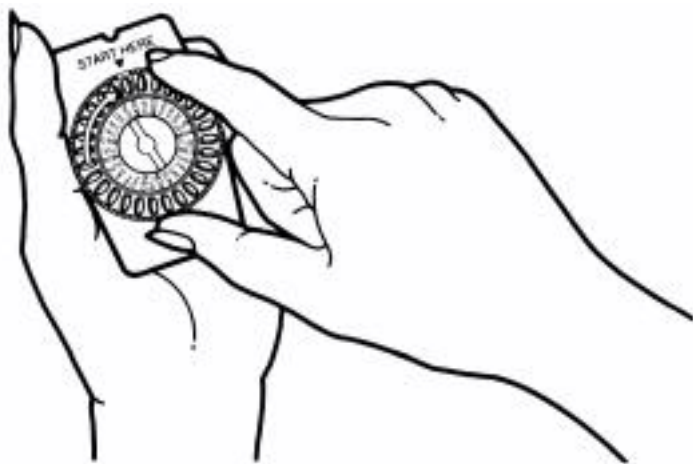
2. **LOOK AT YOUR PILL PACK TO SEE IF IT HAS 21 OR 28 PILLS:**

The *21-pill pack* has 21 “active” brown, white or light-yellow pills (with hormones) to take for 3 weeks, followed by 1 week without pills.

The *28-pill pack* has 21 “active” brown, white or light-yellow pills (with hormones) to take for 3 weeks, followed by 1 week of reminder light-green pills (without hormones).

3. **ALSO FIND:**

1. where on the pack to start taking pills, and
2. in what order to take the pills (follow the arrow).



4. **BE SURE YOU HAVE READY AT ALL TIMES:**

ANOTHER KIND OF BIRTH CONTROL (such as condoms, spermicide or sponge) to use as a back-up in case you miss pills.
AN EXTRA, FULL PILL PACK.

WHEN TO START THE FIRST PACK OF PILLS:

You have a choice of which day to start taking your first pack of pills. Decide with your doctor or clinic which is the best day for you. Pick a time of day which will be easy to remember.

DAY 1 START:

1. Take the first “active” brown pill of the first pack during the *first 24 hours of your period*.
2. You will not need to use a back-up method of birth control, since you are starting the pill at the beginning of your period.

SUNDAY START:

1. Take the first “active” brown pill of the first pack on the *Sunday after your period starts*, even if you are still bleeding. If your period begins on Sunday, start the pack that same day.
2. *Use another method of birth control* as a back-up method if you have sex anytime from the Sunday you start your first pack until the next Sunday (7 days). Condoms, spermicide, or the sponge are good back-up methods of birth control.

WHAT TO DO DURING THE MONTH:

1. **TAKE ONE PILL AT THE SAME TIME EVERY DAY UNTIL THE PACK IS EMPTY.**

Do not skip pills even if you are spotting or bleeding between monthly periods or feel sick to your stomach (nausea).
Do not skip pills even if you do not have sex very often.

2. **WHEN YOU FINISH A PACK OR SWITCH YOUR BRAND OF PILLS:**

21 pills: Wait 7 days to start the next pack. You will probably have your period during that week. Be sure that no more than 7 days pass between 21-day packs.

28 pills: Start the next pack on the day after your last “reminder” pill. Do not wait any days between packs.

WHAT TO DO IF YOU MISS PILLS

The pill may not be as effective if you miss brown, white or light yellow “active” pills, and particularly if you miss the first few brown or the last few light-yellow “active” pills in a pack.

If you **MISS 1** brown, white or light-yellow “active” pill:

1. Take it as soon as you remember. Take the next pill at your regular time. This means you may take 2 pills in 1 day.
2. You do not need to use a back-up birth-control method if you have sex.

If you **MISS 2** brown, white or light-yellow “active” pills in a row in **WEEK 1 OR WEEK 2** of your pack:

1. Take 2 pills on the day you remember and 2 pills the next day.
2. Then take 1 pill a day until you finish the pack.
3. You **MAY BECOME PREGNANT** if you have sex in the *7 days* after you miss pills. You **MUST** use another birth-control method (such as condoms, spermicide, or sponge) as a back-up for those 7 days.

If you **MISS 2** brown, white or light-yellow “active” pills in a row in **THE 3rd WEEK**:

1. ***If you are a Day 1 Starter:***
THROW OUT the rest of the pill pack and start a new pack that same day.
If you are a Sunday Starter:
Keep taking 1 pill every day until Sunday.
On Sunday, THROW OUT the rest of the pack and start a new pack of pills that same day.
2. You may not have your period this month but this is expected. However, if you miss your period 2 months in a row, call your doctor or clinic because you might be pregnant.
3. You **MAY BECOME PREGNANT** if you have sex in the *7 days* after you miss pills. You **MUST** use another birth-control method (such as condoms, spermicide, or sponge) as a back-up for those 7 days.

If you **MISS 3 OR MORE** brown, white or light-yellow “active” pills in a row (during the first 3 weeks):

1. ***If you are a Day 1 Starter:***
THROW OUT the rest of the pill pack and start a new pack that same day.
If you are a Sunday Starter:
Keep taking 1 pill every day until Sunday.
On Sunday, THROW OUT the rest of the pack and start a new pack of pills that same day.
2. You may not have your period this month but this is expected. However, if you miss your period 2 months in a row, call your doctor or clinic because you might be pregnant.
3. You **MAY BECOME PREGNANT** if you have sex in the *7 days* after you miss pills. You **MUST** use another birth-control method (such as condoms, spermicide, or sponge) as a back-up for those 7 days.

A REMINDER FOR THOSE ON 28-DAY PACKS:

If you forget any of the 7 light-green “reminder” pills in Week 4:

THROW AWAY the pills you missed.

Keep taking 1 pill each day until the pack is empty.

You do not need a back-up method if you start your next pack on time.

FINALLY, IF YOU ARE STILL NOT SURE WHAT TO DO ABOUT THE PILLS YOU HAVE MISSED:

Use a BACK-UP METHOD anytime you have sex.

KEEP TAKING ONE PILL EACH DAY until you can reach your doctor or clinic.

Pregnancy due to pill failure

The incidence of pill failure resulting in pregnancy is approximately less than 1.0% if taken every day as directed, but average failure rates are 5%. If you do become pregnant, the risk to the fetus is minimal, but you should stop taking your pills and discuss the pregnancy with your doctor.

Pregnancy after stopping the pill

There may be some delay in becoming pregnant after you stop using oral contraceptives, especially if you had irregular menstrual cycles before you used oral contraceptives. It may be advisable to postpone conception until you begin menstruating regularly once you have stopped taking the pill and desire pregnancy.

There does not appear to be any increase in birth defects in newborn babies when pregnancy occurs soon after stopping the pill.

Overdosage

Serious ill effects have not been reported following ingestion of large doses of oral contraceptives by young children. Overdosage may cause nausea and withdrawal bleeding in females. In case of overdosage, contact your health-care provider or pharmacist.

Other information

Your health-care provider will take a medical and family history before prescribing oral contraceptives and will examine you. The physical examination may be delayed to another time if you request it and the health-care provider believes that it is appropriate to postpone it. You should be reexamined at least once a year. Be sure to inform your health-care provider if there is a family history of any of the conditions listed previously in this leaflet. Be sure to keep all appointments with your health-care provider, because this is a time to determine if there are early signs of side effects of oral-contraceptive use.

Do not use the drug for any condition other than the one for which it was prescribed. This drug has been prescribed specifically for you; do not give it to others who may want birth-control pills.

HEALTH BENEFITS FROM ORAL CONTRACEPTIVES

In addition to preventing pregnancy, use of oral contraceptives may provide certain benefits. They are:

- Menstrual cycles may become more regular.
- Blood flow during menstruation may be lighter, and less iron may be lost. Therefore, anemia due to iron deficiency is less likely to occur.
- Pain or other symptoms during menstruation may be encountered less frequently.
- Ovarian cysts may occur less frequently.
- Ectopic (tubal) pregnancy may occur less frequently.
- Noncancerous cysts or lumps in the breast may occur less frequently.
- Acute pelvic inflammatory disease may occur less frequently.
- Oral-contraceptive use may provide some protection against developing two forms of cancer: cancer of the ovaries and cancer of the lining of the uterus.

If you want more information about birth-control pills, ask your doctor or pharmacist. They have a more technical leaflet called the Professional Labeling which you may wish to read.

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A Wyeth-Ayerst Company
Philadelphia, PA 19101
CI 7461-2

Revised: 01/2006

Distributed by: Wyeth-Ayest Company